



**Comparative Efficacy Of Benzydamine Mouthwash With
Other Mouthwash In Radiation Induced Oral Mucositis:
A Systematic Review**

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ABSTRACT:

Background: Oral mucositis is dreadful side effect of cancer therapy. It occurs in almost all patients who receive radiotherapy/chemotherapy for head and neck cancer. **Objectives:** To compare efficacy of benzydamine mouthwash with other mouthwash in radiation induced oral mucositis, in terms of reduction in severity and pain. **Methods:** Computerized literature searches were performed to identify all published articles in the subject from 1988-2022. Following databases were used: PubMed (MEDLINE), Cochrane, and Google Scholar. Randomized controlled trials were included, that compared benzydamine mouthwash with either placebo or any other mouthwash in patients with radiation induced oral mucositis. Data was extracted in a predefined fashion. **Results:** 351 articles were obtained from electronic search. 203-removed after duplicate examination, 148-reviewed for title and abstract, after which 59-excluded due to

other language. 71-excluded as they were review articles/case reports. 18-examined based on the research question. 12 articles which matched PICO of the review, were included. **Conclusion:** There is sufficient evidence to support superiority of benzydamine mouthwash for prophylaxis and management of radiation induced oral mucositis.

Keywords: Head and Neck Cancer, Radiotherapy, Radiation Induced Oral Mucositis, Benzydamine.

INTRODUCTION:

Oral mucositis (OM) is dreadful side effect of cancer therapy which is inflammatory, painful, and ulcerative.^[1] OM occurs in almost all patients who receives radiotherapy (RT)/chemotherapy (CT) for head and neck cancer.^[2] K12.3 is ICD (International Classification of Diseases) -10 code for OM.^[3] Radiation Induced Oral Mucositis (RIOM) can develop within or after 2 weeks from beginning of RT.^[4] Developmental Stages of RIOM are: Stage 1-Initiation, Stage 2-Upregulation, Stage 3-Signal amplification, Stage 4-Ulceration and Stage 5-Healing.^[5] World Health Organization (WHO) has given grading system for OM which is as follows : Grade 0 (None) - None; Grade 1 (Mild) - Oral soreness, erythema; Grade 2 (Moderate) - Oral erythema, ulcers, patients can eat solids; Grade 3 (Severe) - Oral ulcers, Only liquid diet for patients; Grade 4 (Life threatening) - Oral alimentation not possible.^[6] Mostly, RIOM resolves in 2-4 weeks after stoppage of RT with proper treatment. According to literature, benzydamine is mostly used among anti-inflammatory agents for management of OM.^[7] Thus, this systematic review was undertaken to compare efficacy of benzydamine mouthwash with other mouthwash in RIOM.

AIM:

To compare the efficacy of benzydamine mouthwash with other mouthwash in radiation induced oral mucositis in terms of reduction in severity and pain.

OBJECTIVE:

To study the efficacy of benzydamine mouthwash in management of radiation induced oral mucositis in terms of reduction in severity and pain.

MATERIAL AND METHODS:

Protocol And Registration:

PRISMA guidelines were followed and review was registered on PROSPERO. ID:CRD42022376361.

Eligibility Criteria:

- 1) **Population (P):** Patients diagnosed with RIOM.
- 2) **Intervention (I):** Benzylamine mouthwash
- 3) **Comparator (C):** Other mouthwash, sham placebo.
- 4) **Outcome (O):**

Main:

- Reduction in oral mucositis grading.

Secondary:

- Reduction in pain.

Information Sources:

PubMed (MEDLINE), Cochrane, and Google Scholar from 1988 to 2022.

Search:

Search strategy is shown in **Table 1**.

Study Selection:

Eligibility Criteria Of Included Studies:

1. **Type of Studies:** Randomized Controlled Trials.
2. **Publishing date:** 1st January 1988 to 4th October 2022.
3. **Type of participants:**

Inclusion criteria-

- Patients with RIOM between 18-80 years, irrespective of gender.

Exclusion criteria-

- Studies with unavailable/incomplete data.
- Study designs like clinical case reports, case series, books, animal studies, letter to the editor.

Risk of bias:

Risk of bias was evaluated using RoB2.0 tool (2018) [Figure 1]

RESULT:

Study Selection:

351 articles were obtained from electronic search. 203-removed after duplicate examination. 148-reviewed for title and abstract, after which 59-excluded as they were in other language, 71-excluded as they were review articles and case reports and 18-examined based on research question. 12 articles which matched PICO were included.

Study Characteristics:

12 studies included, listed in Table 2.^[13,14,15,16,17,18,19,20,21,22,23,24]

Location Of Studies:

India^[17, 18, 23], Thailand^[19], New Zealand^[13], Tehran^[15, 16, 21, 22], Turkey^[20], Egypt^[24], North America^[14].

Excluded Studies:

6 studies that are excluded are listed in Table 2.^[25,26,27,28,29,30]

DISCUSSION:

Benzydamine is a non-steroidal anti-inflammatory drug.^[8] It possesses anti-inflammatory, analgesic and anaesthetic properties.^[9] The potential of benzydamine to reduce inflammation and pain and to interact with different inflammation pathways suggests its importance for investigation for RIOM.^[10] According to MASCOO/ISOO guidelines, benzydamine is one of the most important agents for prevention of RIOM.^[11] Benzydamine inhibits production of TNF- α , this topical activity of benzydamine suggests, it's use in different clinical trials which demonstrates role of benzydamine in prevention and management of OM.^[12]

This review is the first to assess the efficacy of benzydamine mouthwash and to compare it with other mouthwash in RIOM. It included 12 studies in which benzydamine mouthwash was used as a treatment modality or as a prophylactic agent for RIOM.

L.P. Samaranayake et al reported that, after 6 weeks of use of benzydamine and chlorhexidine mouthwash, both were equally efficacious in reducing pain and mucositis.^[13] **Joel B et al**^[14], **Khosro M Sheibani et al**^[15] and **A. Kazemian et al**^[16] reported that, when compared with placebo, benzydamine effectively reduced pain, ulceration, erythema and frequency of OM. **Roopshri et al** when compared benzydamine with chlorhexidine, povidone iodine and placebo mouthwash for 6 weeks reported that, benzydamine not only delays progression but also reduces pain in RIOM.^[17] **Madhup Rastogi et al** when compared benzydamine mouthwash with saline for 4 weeks, reported that, benzydamine significantly reduces OM even at doses of >50 Gy.^[18] **Panwadee Putwatana et al** reported that, when benzydamine was compared with glycerin payayor mouthwash for OM, glycerin payayor seemed to be superior to benzydamine for preventing RIOM.^[19] **Ozden Erdem et al** reported that, addition of royal jelly to benzydamine mouthwash significantly improves OM and shortens healing time.^[20] **Mahnaz Sahebamee et al** when compared benzydamine with aloe vera mouthwash for 8 weeks, reported that, both were equally efficacious in alleviating severity of RIOM.^[21] **Shahla Kakoei et al** reported that, when compared with benzydamine, niosomal amitriptyline mouthwash and simple amitriptyline mouthwash were superior in decreasing pain and had local anaesthetic effects on OM.^[22] **Yashna Gupta et al** when compared benzydamine with magic mouthwash for 7 weeks, for prophylaxis of RIOM reported that, magic mouthwash showed better results than benzydamine in reducing severity and pain but there was no statistically significant difference between both.^[23] **Mohamed NH et al** when compared benzydamine mouthwash with oral care (brushing twice a day, flossing and use of alcohol-free mouthwashes) and low-level laser therapy reported that, both benzydamine and low-level laser therapy reduced severity of OM effectively.^[24]

From the above literature it can be stated that, benzydamine hydrochloride (0.15%) mouthwash not just delays progression of OM but also reduces severity and pain associated with RIOM. Furthermore, it can also be stated that, favourable effects of benzydamine was obtained even when radiation dose of 60 Gy was given to patient for 7 weeks of RT. No side effects were reported after use of benzydamine.

CONCLUSION:

From the assessment of studies, for this systematic review it can be concluded that, there is sufficient evidence to support superiority of benzydamine mouthwash for prophylaxis and management of RIOM. Benzydamine hydrochloride (0.15%) helps to reduce the degree, delays progression and also reduces intensity of pain in OM, and hence it is more efficient than any other mouth wash for RIOM. It is effective, safe and well tolerated by patient.

LIMITATIONS OF STUDY:

Only articles published in English language were considered.

FUTURE PROSPECTS:

It is essential that dentists have an understanding of different therapies available for cancer treatment and a sound working knowledge of the options available for prevention and management of the oral sequelae of cancer treatment.

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PRISMA FLOW DIAGRAM

Identification of studies via databases and registers

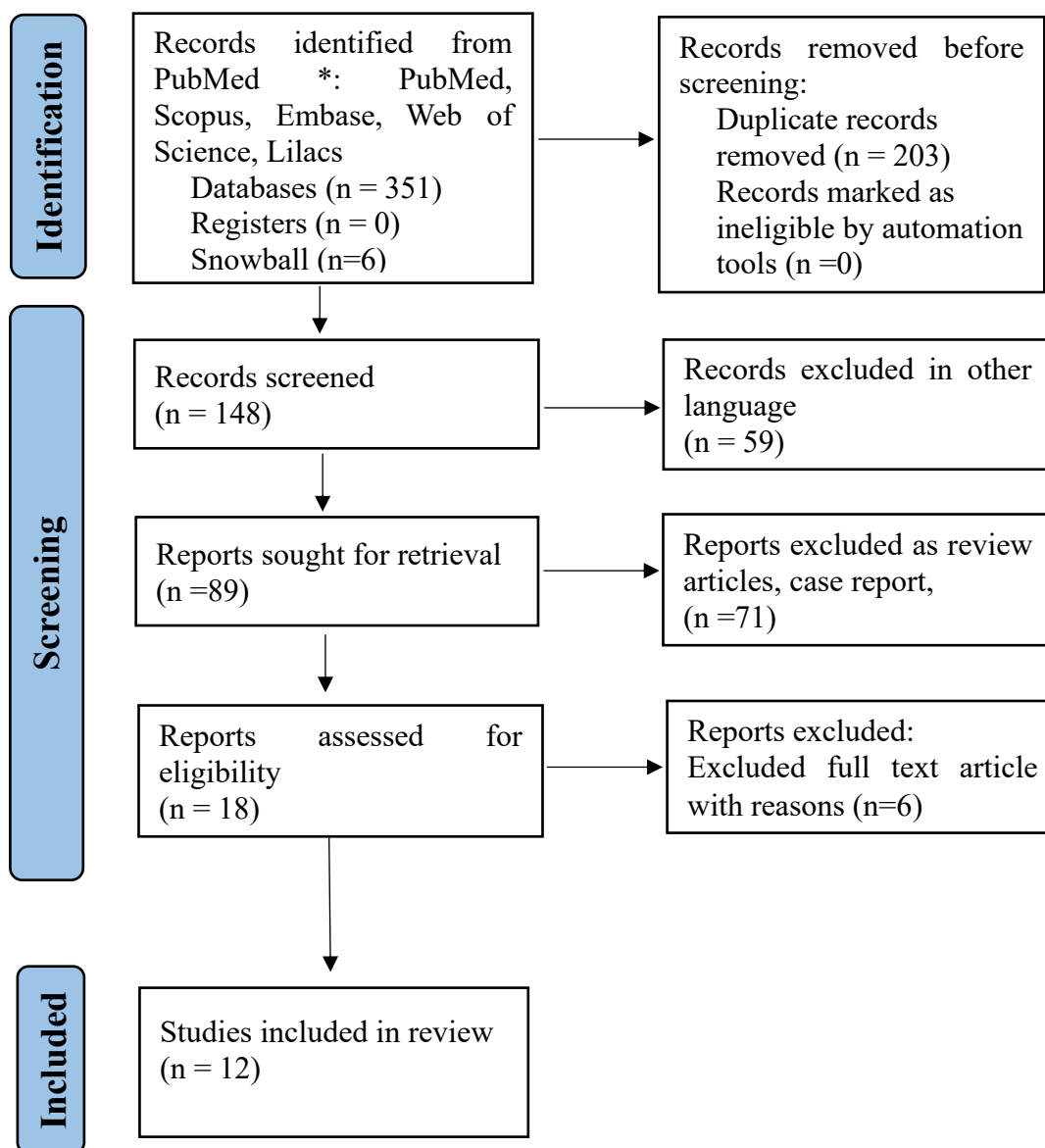


TABLE 1: SEARCH STRATEGY

DATA BASE	SEARCH STRATEGY
PubMed	PubMed search was done using Boolean terms “AND” “OR” Terms used for mucositis:

	<p>Oral mucositis</p> <p>Radiation induced oral mucositis</p> <p>Terms used for Benzydamine:</p> <p>Benzydamine mouthwash</p> <p>Benzydamine hydrochloride mouthwash</p> <p>Terms like “Benzydamine Mouthwash AND Radiation Induced Oral Mucositis” and “Benzydamine Mouthwash OR Radiation Induced Oral Mucositis” was used.</p>
Google scholar	For google scholar the Boolean used were “+” and “-”
Cochrane library	“Benzydamine Mouthwash In Radiation Induced Oral Mucositis” in all text AND “Treatment of Radiation Induced Oral Mucositis with Benzydamine Mouthwash” OR “Treatment of Radiation Induced Oral Mucositis with mouth wash”

TABLE 2: LIST OF INCLUDED AND EXCLUDED STUDIES

Ref No	Title	Ref No	Title	Reason for exclusion
13	The Effect of Chlorhexidine and Benzydamine Mouthwashes on Mucositis Induced by Therapeutic Irradiation.	25	Evaluating the Effectiveness of Topical Application of Pure Natural Honey and Benzydamine	Doctoral dissertation

			Hydrochloride on Radiation - Induced Mucositis.	
14	Benzydamine HCl for Prophylaxis of Radiation-Induced Oral Mucositis.	26	A randomized phase III trial of magic mouthwash and sucralfate versus benzydamine hydrochloride for prophylaxis of radiation-induced oral mucositis in head and neck cancer.	Author did not respond
16	Benzydamine for prophylaxis of radiation-induced oral mucositis in head and neck cancers: a double-blind placebo-controlled randomized clinical trial.	27	Evaluating the Effectiveness of Topical Application of Natural Honey and Benzydamine Hydrochloride in the Management of Radiation Mucositis.	Outcome not specified
19	Relief of Radiation-Induced Oral Mucositis in Head and Neck Cancer.	28	Role of Benzydamine mouthwash in radiation induced oral mucositis-Single blind randomized control study.	Not fulfilling PICO
17	Efficacy of benzydamine hydrochloride, chlorhexidine, and povidone iodine in the treatment of oral mucositis among patients undergoing radiotherapy in head and neck malignancies: A drug trail.	29	Effectiveness of curcumin mouthwash on radiation-induced oral mucositis among head and neck cancer patients: A triple-blind, pilot randomised controlled trial.	Outcome not specified.

20	The Effect of Royal Jelly on Oral Mucositis in Patients Undergoing Radiotherapy and Chemotherapy.	30	Randomized Control Study of the Effects of Turmeric Mouthwash on Oral Health Status, Treatment-Induced Mucositis, and Associated Oral Dysfunctions Among Patients With Head and Neck Cancer.	Author did not respond
21	Comparative Efficacy of Aloe vera and Benzydamine Mouthwashes on Radiation-induced Oral Mucositis: A Triple-blind, Randomised, Controlled Clinical Trial.			
15	Efficacy of benzydamine oral rinse in prevention and management of radiation-induced oral mucositis: A double-blind placebo-controlled randomized clinical trial.			
18	Role of benzydamine hydrochloride in the prevention of oral mucositis in head and neck cancer patients treated with radiotherapy (>50 Gy) with or without chemotherapy.			
22	Comparison the Pain Relief of Amitriptyline Mouthwash with Benzydamine in Oral Mucositis.			
23	Magic Mouth Wash V/s Benzydamine Mouth Wash in Prophylaxis and Treatment of Radiation Induced Oral Mucositis in Patients with Head and Neck Cancers: A Prospective Study.			

24	Low level laser therapy versus benzydamine in prevention and treatment of oral mucositis induced by anticancer treatments (clinical and biochemical study).			
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TABLE 3: EVIDENCE BASED ANALYSIS OF INCLUDED STUDIES

Stud ID	Location	Blinding & Randomization	Age group	Sample size	Duration of the study	Mucositis grading scale	Secondary outcome	Comparison group	Significant outcome
L.P. Samaranaya ke et al 1988 [13]	New Zealand	Unclear	46-72 years	25	6 weeks	4-point likert scale	Pain, Microbial examination	Chlorhexidine	There is little difference between the two mouthwashes both in controlling pain and mucositis or in the oral carriage of the micro-organisms studied.

Joel B et al 2001 [14]	16 centres in North America (15 in the U.S. and 1 in Canada)	Double blind, Unclear	20-78 years	172	2 weeks	4-point likert scale	Use of systemic analgesics, Pain, Erythema, Ulceration	Placebo	Benzydamine delayed the use of systemic analgesics. Benzydamine reduced ulceration and erythema by 30% when compared with placebo. (P=0.006).
A Kazemi an et al 2009 [16]	Tehran	Double blind, Unclear	11-82 years	81	9 weeks	RTOG (Radiation Therapy Oncology Group) grading system	None	Placebo	In benzydamine group, the frequency of grade ≥ 3 mucositis was 43.6% and in

									placebo group the frequency was 78.6% (P=0.001).
Panwadee Putwatana et al 2009 [19]	Bangkok, Thailand	Single blind, Unclear	29-62 years	60	2 weeks	WHO scale	Pain, Xerostomia, Taste alteration, were measured using 4-point likert scale	Glycerine payayor	The mean satisfaction score of the payayor group at the end of the study was significantly higher than that of the benzydamine group (3.55 ± 0.33 vs 2.50 ± 0.55; t =

									2.89, P < .05).
Roopshri et al 2011 [17]	Bhopal (MP), India	Unclear	30-70 years	100	6 weeks	WHO scale	Pain was graded by Lindquist-Hickey scale	Chlorhexidine, Povidone iodine, Placebo	Benzydamine oral rinse (0.15%) reduced the intensity and duration of oral mucositis with a single case of grade 3 mucositis by the end of the 6 th week of RT (4%).
Ozden Erdem	Turkey	Triple blind, Unclear	50-54 years	103	14 days	WHO scale	None	Royal jelly	The mean resolution time of

et al 2014 [20]									mucositis in the royal jelly group was significantly shorter than that of the benzydamine group.
Mahnaz Sahabjee et al 2015 [21]	Tehran	Triple blind and block randomization	26-80 years	26	8 weeks	WHO scale	Burning sensation	Aloe vera	There was no significant difference between Aloe vera and benzydamine groups in terms of mucositis grade (p = 0.09).

Khosro M Sheibani et al 2015 [15]	Tehran, Iran	Double blind, Unclear	18-80 years	51	7 weeks	4-point likert scale	None	Placebo	At the end of 7 th week, the mean score of benzydamine group was less than that of placebo group (1.43 vs 1.98. P=0.001)
Madhup Rastogi et al 2016 [18]	Lucknow, India	No blinding, Computer generated randomization	18-80 years	120	4 weeks	WHO scale	Pain was graded by CTCAE (Common Terminology Criteria for Adverse Events version 4.0)	Saline	Benzydamine mouth rinse lowered the incidence of grade 3 mucositis as compared to saline, 62.1 vs.

									36.4% (p = 0.038) and 51.7 vs. 27.3% (p = 0.043), respectively.
Shahla Kakoei et al 2018 [22]	Kerman, Iran	Double blind, Unclear	14-74 years	60	Not Specified	4-point likert scale	Pain and burning sensation was graded by VAS.	Amitriptyline, or niosomal form of amitriptyline.	There was no significant difference reported, between amitriptyline and benzydamine groups in terms of mucositis grade

									(p< 0.05). 10 min after the use of niosomal form of amitripty line, 95% reduction in pain was observed . 99% reduction in pain reported after the use of simple form of amitripty line (p= 0.04)
Yas hna Gupta et al 2018 [23]	Delhi, India	Unclear	18-57 years	60	8 weeks	4-point likert scale	None	Magic mouth wash	There was no significant difference reported, between magic

									mouthwash and benzydamine mouthwash in terms of mucositis grade.
Nas hwa Helayly Mohamed et al 2022 [24]	Egypt	Triple blind and block randomization	18-80 years	100	7 weeks	WHO scale and National Institute of Cancer-Common Toxicity Criteria (NIC-CTC)	Pain was graded by VAS. TNF- α was measured using ELISA test.	Oral care (brushing twice a day, flossing, and use of alcohol-free mouthwashes.) and Laser	The data extremely support and suggest the prophylactic utilization of benzydamine hydrochloride to reduce OM in cancer-treated patients following a

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									moderate dose of radiation therapy.
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TABLE 4: CONCENTRATION AND FREQUENCY OF BENZYDAMINE MOUTHWASH USED IN INCLUDED STUDIES

Ref No.	Author/Year	Concentration	Frequency of benzydamine mouthwash
13	L.P. Samaranyake et al 1988	0.15%	15 ml of benzydamine mouthwash was used for 30 seconds, twice a day, for 6 weeks.
14	Joel B et al 2001	0.15%	15 ml of benzydamine mouthwash was used for 2 minutes, 4-8 times daily, before and during RT, and for 2 weeks after completion of RT.
16	A Kazemian et al 2009	0.15%	15 ml of benzydamine mouthwash was used for 2 minutes, 4 times a day from the 1 st day of RT to the end of the treatment.
19	Panwadee Putwatana et al 2009	0.15%	15 ml of benzydamine mouthwash was used thrice daily, for 2 weeks.
17	Roopshri et al 2011	0.15%	15 ml of benzydamine mouthwash was used for 30 seconds, 4 times a day at 6 hours interval, for 1 week.
20	Ozden Erdem et al 2014	Not specified	Not specified
21	Mahnaz Sahebamee et al 2015	0.15%	5 ml of benzydamine mouthwash was used, 3 times a day from the 1 st day of RT till 6 weeks.
15	Khosro M Sheibani et al 2015	0.15%	15 ml of benzydamine mouthwash was used for 2 minutes, 4-8 times daily before and during, and for 2 weeks after completion of RT.
18	Madhup Rastogi et al 2016	0.15%	10 ml of benzydamine mouthwash was used for 1 minute, 4-6 times a day for 4 weeks.
22	Shahla Kakoei et al 2018	Not specified	15 ml of benzydamine mouthwash was used for 30 seconds.

23	Yashna Gupta et al 2018	0.15%	5 ml of benzydamine mouthwash was used for 2 minutes, 4 times a day, starting 1 day before RT, and stopping 2 weeks after completion of RT.
24	Nashwa Helaly Mohamed et al 2022	0.15%	15 ml of benzydamine mouthwash was used for 2 min/4-8 times each day till 7 weeks.

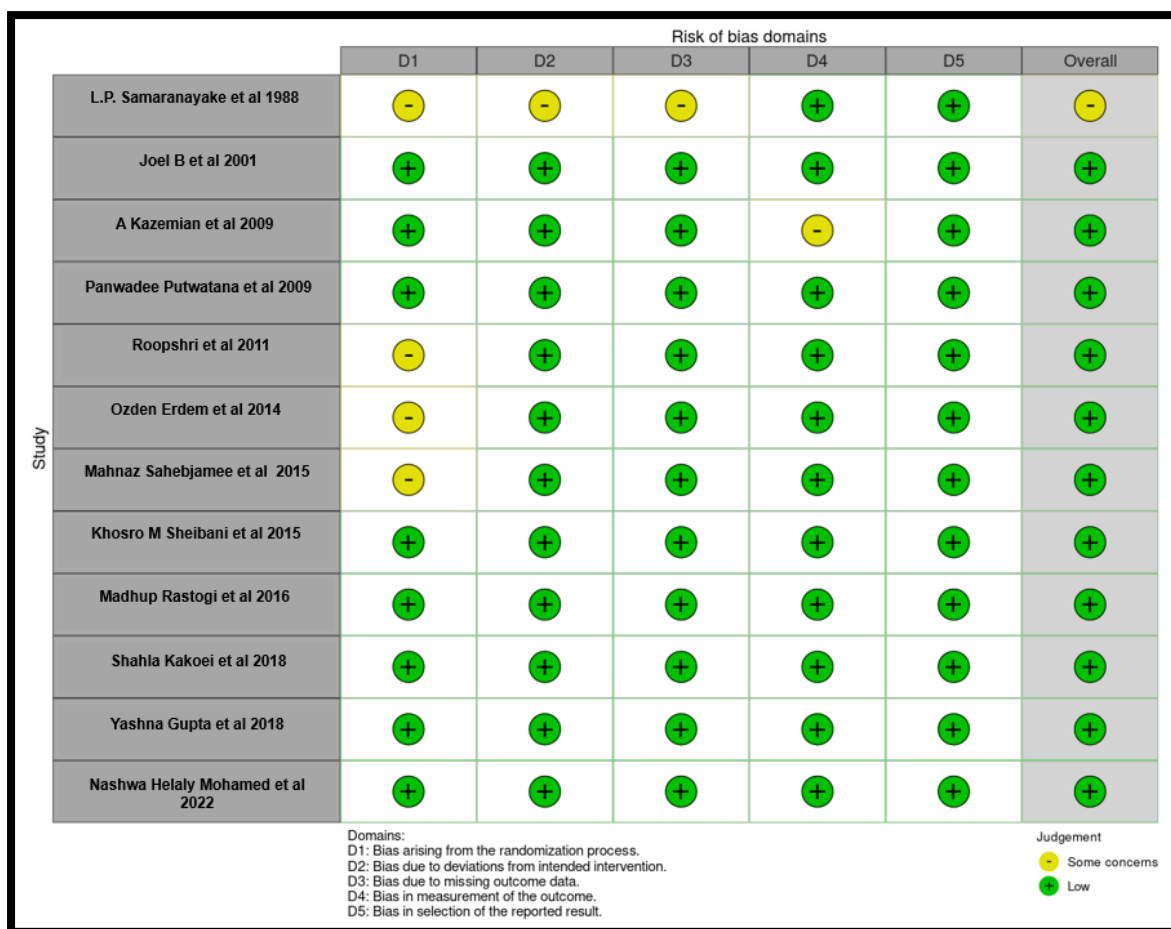


Figure 1: Traffic Light Plot For Risk Of Bias

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